Journal of Applied Electrochemistry (2005) 35:845–849
DOI 10.1007/s10800-005-1433-1

Electroreduction of (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-propane-1,3-diol derivatives. Behaviour of electrogenerated species and applications to organic synthesis

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Received 2 March 2004; accepted in revised form 3 January 2005

Key words: (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-propane-1, 3-diol derivatives, benzoxazine diones, cathodic reduction, electrosynthesis, mercury batch cell, N-sulphonylated phenylhydroxylamines, phenylhydroxylamines

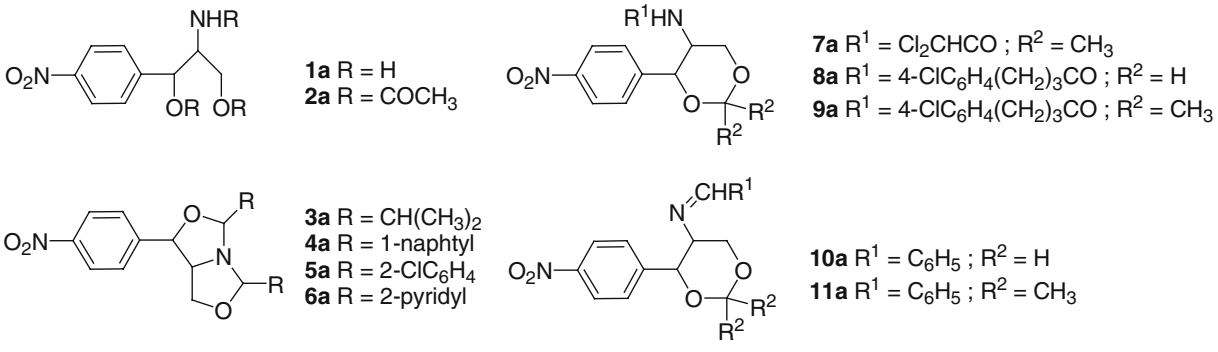
Abstract

Hydroxylamines electrogenerated from (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-propane-1,3-diol derivatives (derivatives of *p*-nitrophenylserinol) are unstable in methanol–acetate buffer and practically stable in acetonitrile–aqueous acetate buffer. This latter medium was used to carry out subsequent reactions *in situ* involving the triacetylated *p*-hydroxylaminophenylserinol and various reagents. An azoxy compound was the major product isolated after reaction with maleic or phthalic anhydrides. In contrast, a benzoxazine dione was normally obtained with phthaloyl dichloride and a N-sulphonylated hydroxylamine was produced with *p*-toluenesulphonyl chloride.

1. Introduction

(1*S*,2*S*)-2-amino-1-(4-nitrophenyl)- propane-1,3-diol (usually known as *p*-nitrophenylserinol, hereafter labelled as *p*-NFS) and its derivatives were studied as possible intermediates in the synthesis of chloramphenicol (chloromycetine) [1–4] or as additives in the rubber industry [5]. Some years ago, various derivatives of *p*-NFS were synthesized and their stereochemistry was studied [6–8]. Because of their potential biological activity they also became of interest for the electrosynthesis of new compounds. The electroreduction products (hydroxylamino compounds) obtained from *p*-NFS and its derivatives (Scheme 1) could be key products in the synthesis of various species with biological potential activities. With this aim in view, we continued our previous investigations in this field [9–11].

Hydroxylamine derivatives can be electrochemically prepared in a batch cell from the corresponding nitro compounds. A good control of the working potential generally allows the synthesis of hydroxylamines in high yields. However, because of a long time scale for electrolyses in batch cells, side reactions can take place; consequently, this type of cells can be only used for the synthesis of stable hydroxylamines. Because phenylhydroxylamines are air sensitive, our interest was the



Scheme 1

in situ trapping of these species with various reagents in order to prepare final products.

2. Experimental

2.1. *Electrochemistry*

All experiments were carried out at room temperature. The solutions were purged with argon or nitrogen.

Polarograms and cyclic voltammograms of nitro compounds 10^{-3} M in methanol or acetonitrile–water (8:1, v/v) containing acetate buffer (0.5 M CH_3CO_2H + 0.5 M CH_3CO_2Li) as electrolyte, were recorded using a BAS 100 potentiostat. Potentials refer to Ag/Ag^+ electrode or saturated calomel electrode (SCE). For cyclic voltammetry, the working electrode was a glassy carbon electrode supplied by BAS Inc. Between each measurements, the working electrode was polished with diamond paste and washed with deionised water.

Coulometric analyses and preparative electrolyses at a mercury pool cathode were performed under potentiostatic conditions in a symetrical cell with two compartments and a SCE electrode as reference electrode [12]. The electrolyses were performed with classical equipment: a scanning potentiostat EG&G Princeton Applied Research Model 362 equipped with a *XY* recorder and connected to an electronic coulometer *Tacussel* IG5N. Electrolyses were monitored by polarography. Controlled potential electrolyses involved 150–200 mg of nitro compound in 120 ml of buffered solution.

2.2. *Starting compounds*

p-NFS **1a** and its derivatives **3a–11a** were prepared according to the procedure of Darabantu et al. [6–8].

In order to avoid secondary reactions with electrophilic reagents after electrolysis, the –OH and $–NH_2$ groups of *p*-NFS **1a** were protected by $N–O^1–O^3$ triple acetylation. Acetic anhydride in excess and pyridine (1 ml) were added to 1 g of *p*-NFS **1a** [13]. The resulting solution was stirred for 24 h at room temperature. The crude product was chromatographed on silica column eluting with a mixture methanol/ether (1:9) to give **2a** in 75% yield. The ^{1}H NMR spectrum of **2a**, recorded in $CDCl_3$, on a Brucker DPI 200 FT spectrometer was consistent with the desired structure. The IR spectra were obtained on a Nicolet type 205 FT-IR apparatus.

(1S,2S)-acetic acid 3-acetoxy-2-acetylamino-1-(4-nitrophenyl)-propyl ester **2a**: M.p: 162–164 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.20 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 6.01 (d, J = 5.3 Hz, 1H), 5.82 (d, J = 9.5 Hz, 1H), 4.66 (m, 1H), 4.04 (AB, 2H), 2.13 (s, 3H), 2.05 (s, 3H), 1.91 (s, 3H). IR (powder in KBr): 3383.5, 3297.7, 3079.4, 2960.2, 1747.6, 1662.4, 1521.7, 1226.0, 1047.1 cm^{-1}. Anal. Calc: C, 53.25; H, 5.36; N, 8.28. Found: C, 53.31; H, 5.41; N, 8.13.

In a similar way the acetic acid 4-nitrobenzyl ester **12a** was prepared from 4-nitrobenzyl alcohol in 82% yield.

Acetic acid 4-nitrobenzyl ester **12a**: M.p: 98–100 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.22 (d, J = 6.8 Hz, 2H), 7.51 (d, J = 6.9 Hz, 2H), 5.20 (s, 2H), 2.17 (s, 3H). IR (powder in KBr): 1736.9, 1516.5, 1448.3, 1341.8, 1233.4, 1047.5, 835.9, 740.1. Anal. Calc: C, 55.39; H, 4.65; N, 7.18. Found: C, 55.65; H, 4.71; N, 7.05.

2.3. *Reduction compounds*

After the electrolysis of nitro compounds **2a** and **12a** in a mixture aqueous acetate buffer-acetonitrile (1:8, v/v), commercially available reagents (maleic or phthalic anhydride, phthaloyl dichloride or *p*-toluenesulphonyl chloride) were added to the resulting solution. The subsequent reactions were monitored by polarography. After a complete disappearance of the anodic wave attributed to the hydroxylamine derivative, the organic solvent was evaporated in vacuo. An aqueous solution of $NaHCO_3$ was added to the acidic residue. The resulting solution was extracted with ether and the organic solvent was dried over magnesium sulfate and evaporated to dryness. The residue was chromatographed on silica.

Azoxy compounds **2c** (54%) and **12c** (65%) were identified as the major products resulting from the reaction between maleic or phthalic anhydride and the hydroxylamino derivatives **2b** and **12b**. A small amount of the azo compound **12d** was also characterized.

Acetic acid 4-(4-acetoxymethyl-phenylazo)-benzyl ester **12d**: ^{1}H RMN (200 MHz, $CDCl_3$): δ 7.93 (d, J = 8.4 Hz, 4H), 7.52 (d, J = 8.3 Hz, 4H), 5.18 (s, 2H), 2.14 (s, 3H).

Acetic acid 4-(4-acetoxymethyl-phenyl-NNO-azoxy)-benzyl ester **12c**: ^{1}H RMN (200 MHz, $CDCl_3$): δ 8.30 (d, J = 8.7 Hz, 2H), 8.17 (d, J = 8.4 Hz, 2H), 7.49 (m, 4H), 5.20 (s, 2H), 5.15(s, 2H), 2.15 (s, 3H), 2.14 (s, 3H). Anal. Calc: C, 63.16; H, 5.26; N, 8.19. Found: C, 63.47; H, 5.12; N, 8.13.

Acetic acid 3-acetoxy-2-acetylamino-3-{4-[-(1,3-diacetoxy-2-acetylamino-propyl)-phenyl-NNO-azoxy]-phenyl}-propyl ester **2c**: (ether/light petroleum, 7:3); ^{1}H RMN (200 MHz, $CDCl_3$): δ 8.28 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.6 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H), 7.45 (m, J = 8.7 Hz, 2H), 6.03 (m, J = 9.6 Hz, 1H), 5.79 (d, J = 9.5 Hz, 1H), 4.69 (m, 1H), 4.07 (m, J = 18.5 Hz, 1H), 2.12 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H); IR (CH_2Cl_2): 3368.6, 2953.7, 1734.9, 1654, 1595.6, 1465.6, 1374.9, 1232.2, 1029.3 cm^{-1}. Anal. Calc: C, 60.00; H, 6.00; N, 4.67. Found: C, 59.87; H, 6.07; N, 4.39.

The coupling reactions between phthaloyl dichloride and the hydroxylamino derivatives **2b** and **12b** afforded benzoxazine diones **2e** (47%) and **12e** (65%).

Acetic acid 4-(1,4-dioxo-1,4-dihydro-benzo[d][1,2]oxazin-3-yl)-benzyl ester **12e**: ^{1}H RMN (200 MHz, $CDCl_3$): δ 8.40 (m, 2H), 8.27 m, 2H), 7.72 (d,

J = 8.4 Hz, 2H) 7.54 (d, J = 8 Hz, 2H), 5.14 (s, 2H), 2.12 (s, 3H). Anal. Calc: C, 65.59; H, 4.18; N, 4.50. Found: C, 65.13; H, 4.17; N, 4.39.

Acetic acid 3-acetoxy-2-acetylamino-1-[4-(1,4-dioxo-1,4-dihydro-benzo[d][1,2]oxazin-3-yl)-phenyl]-propyl ester **2e**: ^{1}H RMN (200 MHz, $CDCl_3$): δ 8.30 (d, J = 8.7 Hz, 2H), 8.16 (d, J = 8.5 Hz, 2H), 7.43 (m, 4H), 6.05 (m, 1H), 5.28 (s, 1H), 4.07 (AB, 2H), 2.14 (s, 3H), 2.07 (s, 3H), 1.96 (s, 3H). Anal. Calc: C, 60.79; H, 4.85; N, 6.17. Found: C, 60.57; H, 4.70; N, 6.12.

By adding *p*-toluenesulphonyl chloride to the hydroxylamino derivative **2b** the sulphonylated hydroxylamine **2f** was obtained in 41% yield.

Acetic acid 3-acetoxy-2-acetylamino-1-{4-[hydroxy-(toluene-4-sulfonyl)-amino]-phenyl}-propyl ester **2f**: M.p. 118–120 °C; ^{1}H RMN (200 MHz, $CDCl_3$): δ 8.90 (s, 1H) 7.31 (d, J = 8.3 Hz, 2H), 7.25 (m, 6H), 5.98 (m, 1H), 5.88 (d, J = 6.7 Hz, 1H), 3.88 (AB, 2H), 2.39 (s, 3H), 2.12 (s, 3H), 2,09 (s, 3H), 2.07 (s, 3H). IR (powder in KBr): 1690.2, 1225.8, 1166.3, 1039.3 cm^{-1}. Anal. Calc: C, 59.19; H, 5.83; N, 6.28. Found: C, 58.87; H, 5.87; N, 6.19.

3. Results and discussion

3.1. *Polarography and cyclic voltammetry*

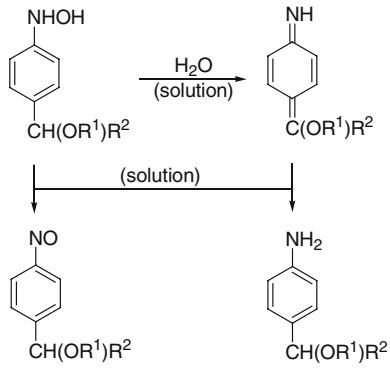
We previously mentioned [14, 15] various factors acting on the electrochemical behaviour of *p*-NFS **1a** (cathode material, medium, pH, presence of inhibitors and substituents). The electrochemical reduction of *p*-NFS appears easier on mercury. In order to establish the reaction mechanisms, the behaviour of *p*-NFS and its derivatives was studied in methanol–acetate buffer and acetonitrile–aqueous acetate buffer.

Polarograms of *p*-NFS **1a** and its derivatives **2a–9a** show a single reduction wave corresponding to a four-electron process ($E_{1/2}$ # −0.45 to −0.60 V vs. SCE, in methanol–acetate buffer). A two-electron wave corresponding to the reduction of the azomethyne group is observed, at more cathodic potential, for compounds **10a** and **11a**.

Cyclic voltammograms at a hanging mercury electrode or a glassy carbon electrode of *p*-NFS **1a** and its derivatives **2a–11a** are characteristic of many nitroarenes in protic media: a reversible system attributed to nitroso-hydroxylamine couple, is observed at less cathodic potential after reduction of the nitro group and scan reversal (Ep_{c1} = −0.67 V Vs. Ag/Ag^+, Ep_a = −0.01 V Vs. Ag/Ag^+ and Ep_{c2} = −0.04 V Vs. Ag/Ag^+ at a mercury electrode, for *p*-NFS **1a** in methanol–acetate buffer). Consequently, the hydroxylamine derivatives appear stable at the time scale (0.1 V s^{-1}) of the cyclic voltammetry.

3.2. *Electrolysis and coulometric data*

In order to prepare new products, nitro compounds **1a–12a** were electrolysed at a mercury cathode. Electrolyses were performed at the plateau of the first cathodic wave in methanol or acetonitrile–water containing acetate buffer (0.5 M CH_3CO_2H + 0.5 M CH_3CO_2Li) as electrolyte. Electrolyses were monitored by polarography and by coulometry.

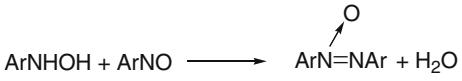


Scheme 2

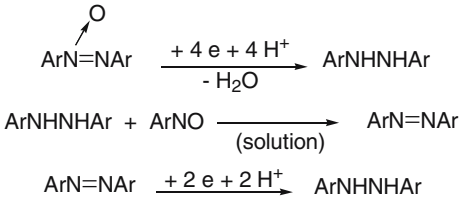
In the two media, we normally observed during electrolyses a decrease of the reduction wave of the nitro group and an increase of the oxidation wave of hydroxylamines **1b–12b**. However, the hydroxylamine derivatives appeared unstable in methanol. An excess of electricity (4.5 F to 5.5 F per mole, according to the substrate) was recorded while a high residual current intensity was persistent. A slow decrease of the oxidation wave was observed in the second part of the electrolysis when several new cathodic waves of low intensities appeared. Small amount of azo and azoxy derivatives near unidentified species were characterized after treatment of the electrolyzed solution.

A slow dehydration of electrogenerated hydroxylamines followed by a redox process (Scheme 2) equivalent to a disproportionation as previously observed for phenylhydroxylamines bearing electrodonating substituents [16–18] can probably explain the instability.

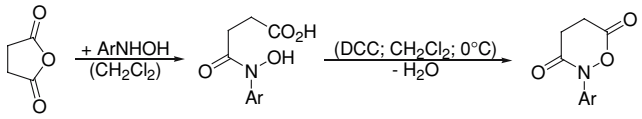
Consequently, a coupling reaction can take place in solution between the hydroxylamino compounds and the nitroso derivatives affording azoxy compounds (Scheme 3) which are cathodically reduced into hydrazo compounds. These last species oxidized by the nitroso compounds in solution give azo derivatives which are



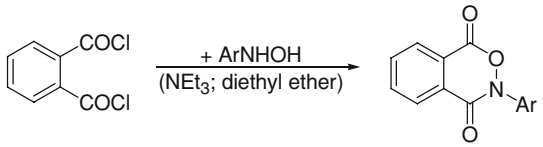
Scheme 3



Scheme 4



Scheme 5



Scheme 6

reducible at the cathode (Scheme 4) as previously shown [19]. A slow disproportionation of the hydrazo derivatives can also occur.

Conversely, the reduction of the nitro compounds **1a–12a** in acetonitrile–water consumed close to 4 F per mole. This last medium in which the hydroxylamine derivatives **1b–12b** appear relatively stable at the time scale of a macroscale electrolysis, was used for subsequent reactions*in situ* involving only the hydroxylamines **2b** and **12b**.

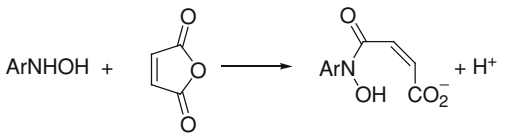
Oxazine diones were previously prepared by reacting cyclic anhydrides [20, 21] or phthaloyl dichloride [22] with arylhydroxylamines in organic solvents as shown in Schemes 5 and 6.

By adding a quasi stoechiometric quantity of maleic or phtalic anhydride to the electrolysed solution of **2b** and **12b**, we observed an immediate disappearance of the anodic wave of the hydroxylamine derivatives and simultaneously a new cathodic wave appeared in the potential range of the starting nitro compounds. This wave was attributed to azoxy derivatives **2c** and **12c** which were isolated, purified and characterized. The ^{1}H-NMR spectra showed the typical signals for azoxy compounds. Similar behaviours were also observed after addition of maleic anhydride to phenylhydroxylamine and *p*-tolylhydroxylamine in the same medium (Table 1).

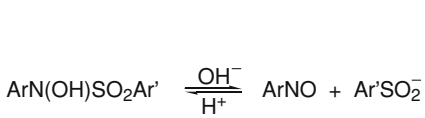
The azoxy derivatives near unidentified products (except trace amount of azo derivative **12d**) obtained after addition of maleic or phthalic anhydride to hydroxylamines were unexpected. As shown in Scheme 3, the azoxy derivatives generally result from a coupling reaction between hydroxylamine and nitroso compounds. The azoxy formation in the presence of

Table 1. Azoxy compounds isolated after adding maleic anhydride to a solution of hydroxylamines (ArNHOH) electrogenerated in acetonitrile–aqueous acetate buffer

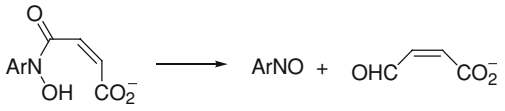
Ar	Yield/%
C_6H_5	24
p-$CH_3C_6H_4$	47
p-$CH_3COOCH_2C_6H_4$ (12c)	65
p-$CH_3COOCH_2CH(NHCOCH_3)$ $CH(OCOCH_3)C_6H_4$ (2c)	54



Scheme 7



Scheme 8



Scheme 9

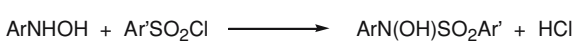
anhydrides, necessary involves a direct or indirect redox reaction between these species and hydroxylamines. A disproportionation of hydroxylamines into nitroso and amino derivatives seems unlikely. Because the electrolyzed solution remained all the time under N_2 atmosphere an oxidation of hydroxylamine by air is excluded. The azoxy formation could probably result from an instability, in the medium, of hydroxamic acids produced according to Scheme 7.

By analogy with the chemical evolution of N-sulphonylated phenylhydroxylamines in neutral or basic media [23, 24] which afford nitroso compounds and sulfinate anions (Scheme 8), an internal redox reaction could explain the nitroso formation (Scheme 9). The presence of aldehydic products in solution could support our hypothesis. However, these species were not detected. Subsequent reactions affording unidentified products are conceivable.

Conversely, new benzoxazines diones derivatives were normally obtained by adding stoechiometric amounts of phthaloyle dichloride to a solution of hydroxylamines **2b** and **12b** (65 and 47% yields, respectively). After addition of phthaloyle dichloride to the electrolyzed solution, we observed a slow disappearance of the anodic wave of the hydroxylamine and simultaneously, the appearance of a new cathodic wave located at more negative potential than for the starting nitro compound. This wave was attributed to the reduction of the benzoxazine dione.

The addition of arylsulphonyl chlorides to phenylhydroxylamines in acidic aqueous or organic solvents gives N-sulphonylated phenylhydroxylamines [23] as shown in Scheme 10.

The same products can be obtained by adding arylsulphinic acids to nitrosobenzenes in acidic aqueous–alcoholic media [24] (Scheme 8).



Scheme 10

The addition of a stoechiometric amount of *p*-toluenesuphonyle chloride to a solution of hydroxylamine **2b** in acetonitrile–aqueous acetate buffer led to a rapid disappearance of the anodic wave. The corresponding N-sulphonylhydroxylamine **2d** was isolated in 44% yield and characterized. This product is identical with the one obtained by adding sodium *p*-toluenesulphinate to a solution of the nitroso compound electrogenerated from **2a** [25] in a ''redox'' flow cell equipped with to consecutive porous electrodes of opposite polarities [26–28].

4. Conclusion

Hydroxylamines produced from cathodic reduction of *p*-NFS derivatives present a poor chemical stability in methanol–acetate buffer. Because of a higher stability observed for these reduced species in acetonitrile–aqueous acetate buffer, subsequent reactions with electrophilic reagents can be performed *in situ*. Surprisingly, the expected hydroxamic acids which could be precursors of oxazine diones, were not obtained by adding cyclic anhydrides to a solution of electrogenerated hydroxylamines in acetonitrile–aqueous acetate buffer and azoxy compounds were the major products. In contrast, benzoxazine diones can be normally prepared in this medium by adding phthaloyl dichloride to hydroxylamines resulting from acetylated *p*-nitrobenzylalcohol **12a** and triacetylated *p*-NFS **2a**. By this way, benzoxazinediones resulting from various *p*-NFS derivatives could be obtained in order to study their biological activities. Moreover, the addition of *p*-toluenesulphonyl chloride to the hydroxylamine electrogenerated from the triacetylated *p*-NFS **2a** gives a N-sulphonylated hydroxylamine **2d**. This latter species can be also obtained by a reversible addition [24] of the nitroso derivatives and *p*-toluenesuphinic acid, so that the reaction of an arylsulphonyl chloride and a phenylhydroxylamine can be an alternative route to the preparation of a nitroso compound.

Acknowledgements

We are grateful for financial support from the French Government (for C.V.C.) and to the Romanian Ministry of Research (Research Grant CERES 130/2001).

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